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The neurobiology of circadian rhythms

Eddy A. Van der Zee^a, Gretha J. Boersma^b and Roelof A. Hut^c

^aDepartments of Molecular Neurobiology,

^bNeuroendocrinology and ^cChronobiology, Center of Behavioral and Cognitive Neurosciences, University of Groningen, Haren, The Netherlands

Correspondence to Eddy A. Van der Zee, Molecular Neurobiology, Center of Behavioral and Cognitive Neurosciences, University of Groningen, Kerklaan 30, 9751 NN Haren, The Netherlands
Tel: +31 0 50 3632062; e-mail: e.a.van.der.zee@rug.nl

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Purpose of review

There is growing awareness of the importance of circadian rhythmicity in various research fields. Exciting developments are ongoing in the field of circadian neurobiology linked to sleep, food intake, and memory. With the current knowledge of critical 'clock genes' (genes found to be involved in the generation of circadian rhythms) and novel techniques for imaging cyclic events in brain and peripheral tissue, this field of research is rapidly expanding. We reviewed only some of the highlights of the past year, and placed these findings into a mutual circadian perspective.

Recent findings

Recent findings on the organization of the circadian clock systems are addressed, ranging from the retina to the suprachiasmatic nucleus and peripheral organs. Novel developments in sleep, food intake, and memory research linked to circadian aspects are discussed.

Summary

The neurobiology of circadian rhythms is pivotal to the orchestration of the temporal organization of an individual's physiology and behavior. Endogenous circadian timing systems underlie coupling and uncoupling mechanisms of many neuronal and physiological processes, the latter possibly inducing health risks to the organism. The integration of sleep, food intake and memory in a circadian setting has clear potential as a systems neurobiology line of research.

Keywords

energy homeostasis, memory, sleep, suprachiasmatic nucleus

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Introduction

Circadian rhythms allow the organism to anticipate and respond to environmental changes and adjust accordingly. Circadian timekeeping systems in mammals are known to be organized in a hierarchical multioscillator network with the suprachiasmatic nucleus (SCN) acting as the central pacemaker (Fig. 1). This brain region, located in the ventral part of the hypothalamus, drives daily (circadian) rhythms. In several neurobiological aspects the SCN is a remarkable brain region, with an unusual high level of intercellular communication. It can be viewed as a programmable and flexible internal time-keeping system. Data on the expression of proteins novel to the SCN appear regularly. For example, the SCN was shown to be one of the few adult brain regions with dense doublecortin (DCX) expression [1]. DCX plays a role in neuronal and synaptic plasticity, and DCX may mediate rhythmic changes in SCN synaptic organization that underlie day/night changes in electrical signaling. Such reports make clear that the neurochemistry of the master clock has not been fully mapped yet.

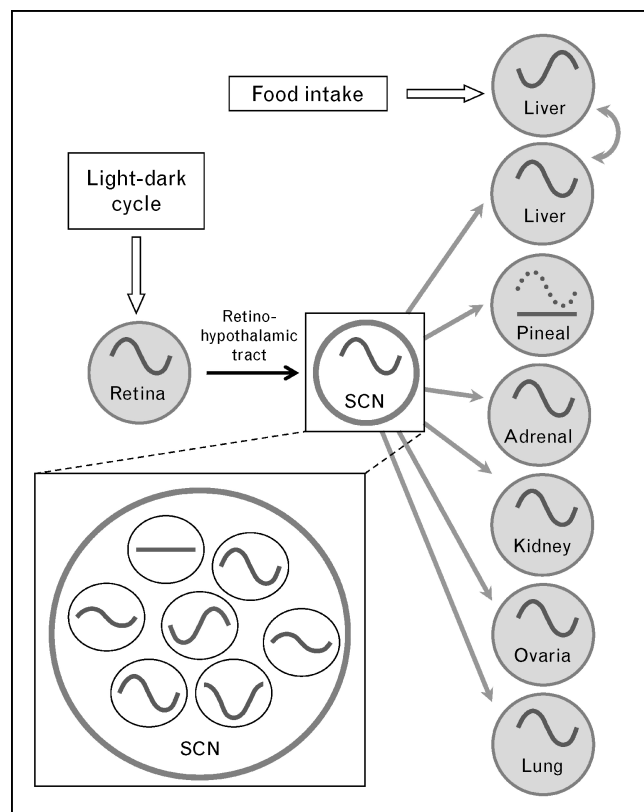
Nowadays, it has been shown that circadian oscillators exist in most regions of the brain, the retina, and many

peripheral tissues such as the liver [2] (Fig. 1). It also became apparent that most body tissues contain circadian oscillation mechanisms that may uncouple from the SCN's influence only under specific conditions. The food entrainable oscillator (FEO), which becomes apparent under restricted feeding conditions, is illustrative for an uncoupling process from the SCN. Restricted feeding conditions affect clock gene expression in many regions of the hypothalamus [3], but not all known clock genes seem to be involved [4]. Although the opposite has been suggested [5], it is now clear that the FEO does not depend on the canonical circadian molecular network and that it cannot be localized to the dorsomedial hypothalamus (DMH) [6[•]]. Possibly, the FEO does not reside in a single brain region but in a neuronal network. This network could be the septo-hippocampal-thalamo-hypothalamic circuit, which was found to be activated 3 h before food anticipation [7[•]]. Nevertheless, the quest for finding the site and mechanism of the FEO remains open.

Circadian rhythms and the retina

Zeitgebers (external stimuli phase shifting and entraining the intrinsic circadian rhythm) synchronize the circadian

Figure 1 Circadian timekeeping systems



The suprachiasmatic nucleus (SCN) receives retinal light input, and endows its rhythm on various peripheral organs. The pineal gland fully depends on SCN input for circadian rhythmicity, whereas the liver can uncouple in part from the master clock under restricted feeding conditions. Within the SCN, individual cells or cell clusters can be out of phase with each other. Occasionally, nonrhythmic cells can be found as well.

rhythms to the environment, with light being critical for the SCN and food timing for the FEO. Within the SCN, neurons generate oscillations of a period of approximately 24h that are synchronized (entrained) to the external light/dark cycle via light input from the retina. The observation of light entrained retinally-degenerated mice led to the discovery of the novel photopigment melanopsin [8,9], which was shown to be the prime photopigment driving circadian light entrainment and other nonimage forming light responses. Melanopsin is found in intrinsically photosensitive retinal ganglion cells and in a novel human cone type [10]. The bi-stability of melanopsin (similar to insect opsins) [11,12,13•] opens the possibility of photosensitization as a tool to enhance circadian entrainment.

The circadian oscillator in the retina has not yet been located to a specific cell type, but it is essential for rhythms in retinal sensitivity [14[•],15]. This observation may in part explain the mechanism by which the circadian system modulates its own photic input [16,17].

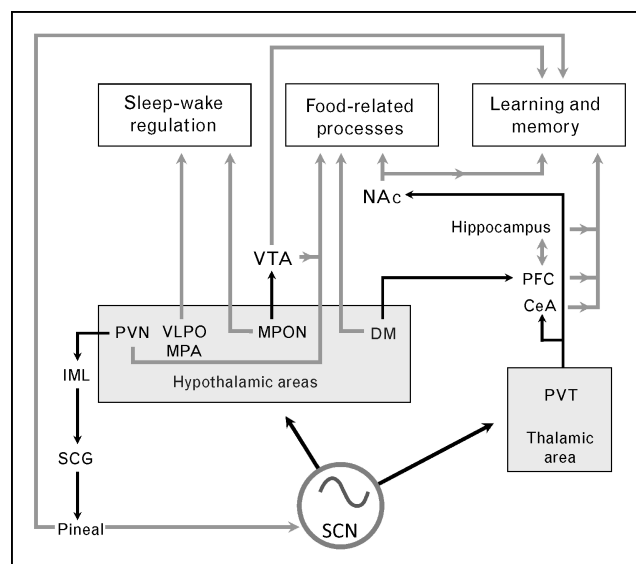
Circadian clocks and output pathways

Essential in the neurobiology of circadian rhythms is the wiring of the SCN. Gradually it is better known how the SCN communicates to other brain regions to impart or entrain circadian rhythmicity in behavioral and physiological processes (Fig. 2; [18] and references therein). The SCN transmits light information to peripheral organs such as the liver via autonomic innervation [19], which can lead to changes in liver clock gene expression unrelated to the expression of liver output genes [20]. The functional relevance of such communication between the SCN and peripheral organs is as yet unknown.

Recently, an interesting novel SCN output pathway to the ventral tegmental area (VTA) via the median preoptic nucleus (MPON) has been described [21[•]]. This projection may function as the circadian regulator of behavioral processes such as arousal and motivation, further bridging well known behavioral observations on reward-related actions and circadian rhythmicity.

Peripheral tissues exhibit their own distinct pattern of phase distribution of clock and clock-controlled genes (e.g. [22]). Why are peripheral clocks needed in the presence of a central brain clock? One explanation is that these organs require independence from the SCN-derived rhythm to function optimally. An example is the

Figure 2 Suprachiasmatic nucleus connections within the brain



CeA, central amygdala; DM, dorsomedial hypothalamus; IML, intermediolateral column of the spinal cord; MPA, medial preoptic area; MPOI, median preoptic nucleus; NAc, nucleus accumbens; PFC, prefrontal cortex; PVN, paraventricular nucleus; PVT, thalamic paraventricular nucleus; SCG, superior cervical ganglion; SCN, suprachiasmatic nucleus; VLPO, ventrolateral preoptic area; VTA, ventral tegmental area. Global scheme of SCN output pathways. Black arrows indicate direct projections. Grey arrows represent functional connections.

finding of the liver clock, driving a daily rhythm of hepatic glucose export that counterbalances daily food intake during sleep [7[•]]. Another example is the hippocampus, pivotal in neuronal plasticity, learning, and memory processes, which shows rhythmic gene expression relatively independent of the SCN (Fig. 2). This allows for the initiation of intrinsic rhythms necessary for time-of-day dependent memory formation, which can and probably needs to be desynchronized from the SCN rhythm.

Circadian rhythms and sleep

Perhaps one of the most conspicuous features of the circadian system is sleep–wake cycle regulation. Although the fundamental function of sleep is one of the most important open questions in neurobiology [23], several recent insights shed light on its regulatory pathways. The SCN is essential in sleep timing and the dorsomedial aspect of the SCN seems specific for the regulation of rapid eye movement sleep [24]. A direct influence of light on sleep architecture is mediated by melanopsin containing retinal ganglion cells. Melanopsin knock-out mice (OPN4^{-/-}) show disrupted sleep architecture [25–27] which might be explained by direct projections of melanopsin containing ganglion cells to the ventrolateral pre-optic nucleus (VLPO) [28], a hypothalamic area involved in sleep–wake regulation via GABA-ergic projections to lateral hypothalamic orexin (hypocretin) neurons [29,30]. Surprisingly, sleep architecture is also affected by genetic make-up [31–33], and circadian clock genes were found to regulate both circadian and homeostatic components of sleep regulation [34,35]. Insights in molecular sleep regulation and circadian interactions arise from *Drosophila* studies [36–38]. Translation of these findings to mammalian sleep regulation might be a hazardous operation, partly because different definitions of sleep are used in both fields.

Circadian rhythms, energy metabolism and food intake

The exact role of the clock genes in food intake regulation is currently being elucidated. Per2^{-/-} mice were found to lack the typical light/dark food intake pattern. Additionally, these Per2^{-/-} mice do not develop food anticipatory behavior, whereas Per1^{-/-} and wild type mice do [39]. Furthermore, Per2^{-/-} mice lack the α -melanin stimulating hormone (α -MSH) pulse (a neuropeptide inhibiting food intake during the light phase), typically seen before the light phase fasting period [40].

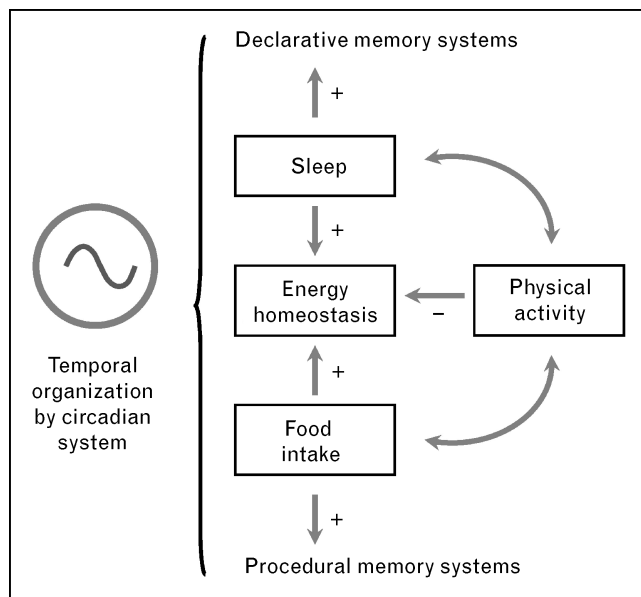
Roles for circadian clocks in energy balance and in the pathological consequences of its disturbance have been suggested. Several studies show that sleep loss leads to increased metabolic syndrome risk (reviewed in [41]).

Additionally, misalignment of circadian and behavioral cycles, as is seen in shift work, induces a risk for diabetes and cardiovascular disease [42[•]], and neuronal PAS domain protein 2 and Per2 clock gene mutations were also linked to metabolic syndrome [43]. Evidently, the circadian clock influences an individual's metabolic well being; however, the reverse also seems true. Deregulation of energy balance, as in metabolic syndrome, altered the expression of several clock genes in brainstem and liver [44,45[•]]. It remains debatable whether circadian misalignment is cause or consequence of metabolic diseases.

Apart from the mentioned interactions between food intake and circadian rhythmicity, a common link between circadian oscillators and food anticipation may be found in the brain reward pathway. Circadian mechanisms are important for the development and expression of reward-related behavior. Withdrawal from chronic treatment results in desynchronization from the SCN rhythm in reward-related brain regions [46]. The suggested link between feeding and reward evokes contradicting views on whether hyper-responsiveness or hypo-responsiveness of the reward system leads to overeating (reviewed in [47]). This contradiction might be explained by a differential effect on anticipatory, circadian regulated food intake, and consummatory feeding behavior [48[•]]. The notion of a robust influence of circadian oscillators on food intake anticipation in combination with the correlation between food anticipatory activity and the reward system suggests an interaction between circadian rhythmicity, reward, and energy metabolism (Fig. 3). This interaction may be mediated by orexin, an orexigenic neuropeptide that stimulates food intake and wakefulness. In Orexin^{-/-} mice cataplexy was powerfully triggered by anticipation of highly rewarding meals, whereas cataplexy was rarely triggered by standard meals, suggesting a role of the reward system in the feeding–wakefulness interaction [49[•]].

Circadian rhythms, learning and memory

The gap in our understanding of how the biological clock and circadian rhythms affect memory processes is being bridged. In general, the sleep–wake cycle supports acquisition (learning) during wakefulness, and promotes memory consolidation during sleep. In *Drosophila*, new findings demonstrate that synaptic proteins increase during wakefulness and decline during sleep [50[•]], which coincides with increasing and decreasing synapse numbers [51[•]]. These studies support the synaptic downscaling hypothesis as a function of sleep. Disruption of sleep–wake patterns and circadian organization of behavior are detrimental to memory. For example, in arrhythmic Siberian hamsters, delayed novel-object learning was impaired [52]. This suggests that hippocampal-dependent learning

Figure 3 Circadian control of activity, energy homeostasis and memory

The reciprocal crosstalk between the circadian timing system, sleep–wake regulation and metabolic regulation is crucial for an organism's well being. It should be noted that memory, gluing past, present, and future, on which many decisions and actions of an organism in maintaining energy homeostasis are based, is directly linked to this crosstalk. Sleep notably promotes declarative memory processing, and reward elements of food intake are often memorized via procedural memory systems.

requires a functional circadian system. SCN lesions in Golden hamsters did not prevent circadian modulation of conditioned place preference, indicative for extra-SCN rhythms underlying this modulation [53•]. These rhythms may be induced by the above-mentioned septo-hippocampal-thalamo-hypothalamic circuit underlying motivated behavior.

In an attempt to further decipher the role of clock genes in learning and memory, Jilg *et al.* [54••] studied *Per1*^{−/−} mice for hippocampus-dependent learning. These *Per1*^{−/−} mice failed to master this task. In contrast, *Cry1*^{−/−}*Cry2*^{−/−} mice successfully learned a spatial task [55•]. These *Cry1*^{−/−}*Cry2*^{−/−} mice, however, failed to associate time and place, an association most likely made by the hippocampus possibly under initial support of the SCN. This indicates clock-gene specific actions underlying certain learning and memory functions, which might relate to specific learning and memory problems in humans.

Most brain regions critically involved in learning and memory are relatively indirectly connected to the SCN (Fig. 1), for example via the SCN-mediated melatonin rhythm. Adult hippocampal neurogenesis (involved in hippocampal memory processes [56,57]) is positively influenced by melatonin promoted cell survival [58]. Another link between melatonin and memory was shown

in the diurnal zebrafish, in which melatonin suppressed nighttime memory formation [59]. Other learning and memory-related areas such as the prefrontal cortex and central amygdala (CeA) receive SCN input via the thalamic paraventricular nucleus (PVT). Rhythmic expression of *Per2* in the CeA is normally synchronized to rhythms of the SCN. However, perturbations of motivational state, energy balance, or stressors affect the CeA rhythm rather than the SCN rhythm [60•]. As a consequence, both intrinsic rhythms become uncoupled. In line with these findings, Neto *et al.* [61•] showed that disruption of circadian rhythms selectively impairs emotional components of memory related to fear and risk evaluation, linking once more circadian rhythm disturbances to mood disorders.

Finally, it should be noted that circadian contributions to learning and memory performance are often underestimated. For one, acquiring new information (training) may act as a Zeitgeber and time stamp, either at the level of the hippocampus, the SCN, or both in mutual interaction [62,63••]. Hence, daily training sessions at random times of day may cause suboptimal memory performance.

Conclusion

The neurobiology of circadian rhythms provides the temporal organization of all basic aspects of an individual. Deregulation of circadian systems is linked to a broad variety of neurological disorders and other human conditions including obesity, anorexia nervosa, cardiovascular and mood disorders, and disturbances in memory and sleep. Further study on the neurobiology of circadian rhythms is needed to allow integration of different neurobiological disciplines and the establishment of circadian systems neurobiology (Fig. 3). One example of the advantage of this knowledge is the development of a 'molecular-timetable method' via blood analysis. This will lead to chronotherapy and personalized medication [64•], even more so when pushed forward to an organ-specific read out.

Acknowledgements

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